

membered carbocyclic or heterocyclic ring contg. 1 or 2 of N, O and S; R9-R12 = H, NO<sub>2</sub>, CF<sub>3</sub>, opt. substd. Ph, CN, CO<sub>2</sub>R<sub>8</sub>, COR<sub>8</sub>, C(=S)R<sub>8</sub>, C(=NH)R<sub>8</sub>, SO<sub>2</sub>R<sub>8</sub>, halo, 1-8C alkyl, 1-8C alkoxy, thio, 1-8C alkylthio, OH, 1-8C alkanoyl, 1-8C alkanoyloxy or NR<sub>5</sub>R<sub>6</sub>; or when adjacent R<sub>9</sub>+R<sub>10</sub> = methylene dioxy; n = 0-3; or NR<sub>5</sub>R<sub>6</sub> completes a 3-6C ring opt. contg. 1 of N, O or S; or NR<sub>1</sub>R<sub>2</sub> and NR<sub>3</sub>R<sub>4</sub> = N=CHR<sub>8</sub>, N=C(Me)R<sub>8</sub> or N=C(NH<sub>2</sub>)R<sub>8</sub> or complete a 3-6C ring opt. contg. 1 or 2 of O, N or S; or R<sub>1</sub>, R<sub>3</sub> = C(=O)R<sub>8</sub>, C(O)OR<sub>8</sub>, C(=S)R<sub>8</sub>, C(=NH)R<sub>8</sub>, SO<sub>2</sub>R<sub>8</sub> or a gp. of formula (ii); x = 0 or 1; y = 1-3; R<sub>8</sub> = H, opt. NR<sub>5</sub>R<sub>6</sub> substd. 1-8C alkyl, 2-8C alkenyl or 2-8C alkynyl, 3-10C cycloalkyl opt. contg. 1 of O, N or S, (i), gp. of formula (iii) or NR<sub>5</sub>R<sub>6</sub>; Ar, Ar' = Ph, imidazolyl, pyrrolyl, pyridyl, pyrimidyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, pyrazinyl, thiazolyl, oxazolyl, isoxazolyl, furanyl, thienyl or naphthyl, all opt. substd. by R<sub>9</sub>-R<sub>12</sub>; provided that when X = N and B = NR<sub>3</sub>R<sub>4</sub> then one of R<sub>3</sub> and R<sub>4</sub> is other than H.

USE - (I) are **inhibitors** of protein tyrosine kinase. They are used for treating vascular **smooth muscle** proliferative disease including atherosclerosis and post-surgical **restenosis**, **inhibiting** cell proliferation and migration, treating psoriasis, **inhibiting** epidermal growth factor receptor tyrosine kinase (TK), Erb-B2 or Erb-B3 or **Erb-B4**, TK, protein TK, C-Src TKprV-SrcTK, **inhibiting** basic and/or acidic fibroblast growth factor receptor TK, treating bacterial infections, treating **restenosis** esp. of coronary arteries following balloon angioplasty, **inhibiting** stenosis following organ transplant, **inhibiting** bypass graft **stenosis**, **inhibiting** stenosis following venous graft, **inhibiting** restenosis of peripheral vessels following angioplasty and **inhibiting** platelet-deriv. growth factor receptor TK (all claimed). (I) are also used in treating cancer and leukaemia. The dosage of (I) is 1-100mg/kg/day. The adult dose is 50-800mg/day. A unit dose prepn. contains 0.1-500 (pref. 0.5-100)mg (I). Cpd. may be admin. in single or multiple doses orally parenterally.

Dwg.0/0

FS

CPI

FA

AB; GI; DCN

MC

CPI: B06-D07; B06-D08; B14-A01; B14-D06; B14-F07; B14-N17C

=> d his

(FILE 'HOME' ENTERED AT 08:30:37 ON 21 JAN 2003)  
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:30:54 ON 21 JAN 2003

	E	ERB
L1	276	S E119
L2	3	S ERB B4
L3	310	S ERBB 4
L4	452	S L1-L3
L5	9	S L4 AND SMOOTH(L)MUSCLE(L)CELL
	E	CELL MIGRATION/CT
L6	4088	S E4-E13
	E	E3+ALL
L7	11558	S E1+NT
	E	E10+ALL
	E	CELL PROLIFERATION/CT
L8	12600	S E4-E10
	E	E3+ALL
L9	49797	S E1+NT
	E	E4+ALL
L10	26908	S E5+NT
	E	E40+ALL

L11 12675 S E6+ALL  
 L12 54568 S E3,E2+NT  
 L13 103 S E1+NT  
 L14 26 S L4 AND L6-L12  
 L15 1 S L13 AND ANTIBOD?  
 E RESTENOSIS/CT  
 E E3+ALL  
 L16 2714 S E2,E3  
 E STENOSIS/CT  
 E E4+ALL  
 L17 806 S E2  
 L18 8117 S RESTENOS? OR STENOS?  
 L19 8 S L4 AND L16-L18  
 SEL DN AN 2 7  
 L20 2 S E1-E6  
 SEL DN AN L5 1 8  
 L21 2 S E7-E12  
 L22 3 S L15,L20,L21  
 E GERRITSEN M/AU  
 L23 125 S E3,E5,E13,E14  
 E SLIWKOWSKI M/AU  
 L24 80 S E3,E5-E8  
 E GENETEC/PA,CS  
 E GENETECH  
 E GENETECH/PA,CS  
 E GENETEC/PA,CS  
 E GENENTEC/PA,CS  
 L25 3390 S E4-E65  
 L26 31 S L4 AND L23-L25  
 L27 1 S L22 AND L26  
 L28 3 S L22,L27  
 L29 30 S L26 NOT L28  
 SEL DN AN L29 3 5 6 10 14 17 21 24  
 L30 8 S L29 AND E1-E24  
 L31 11 S L28,L30  
 L32 11 S L31 AND L1-L31  
 L33 11 S L32 AND (ANTAGON? OR INHIBIT? OR BLOCK? OR ?MODULAT? OR ?PROL  
 E BLOOD VESSEL/CT  
 L34 15 S E61+NT AND L4  
 L35 0 S E94+NT AND L4  
 E URINARY/CT  
 L36 30 S E15+NT AND L4  
 L37 12 S L36 AND BLADDER  
 L38 12 S BLADDER#/CW AND L4  
 E ARTERY/CT  
 L39 6 S E6-E16 AND L4  
 L40 2 S E111-E119 AND L4  
 L41 10 S E110+NT AND L4  
 E RESPIRATORY TRACT/CT  
 L42 4 S E3-E41 AND L4  
 L43 35 S E3+NT AND L4  
 E RECOMBINANT/CT  
 E E5+ALL  
 E E2+ALL  
 L44 1 S E3,E2 AND L4  
 E FUSION/CT  
 L45 19 S E25+NT AND L4  
 L46 70 S L34,L37-L45  
 L47 24 S L46 AND (?MIGRAT? OR ?PROLIFERAT?)  
 SEL DN AN 6 19 20  
 L48 3 S L47 AND E1-E9  
 L49 12 S L33,L48

L50 39 S L46 NOT L47,L49,L5,L14,L19-L22,L28,L31,L32  
SEL DN AN 11 24 39  
L51 3 S L50 AND E10-E18  
L52 15 S L49,L51 AND L1-L51

FILE 'HCAPLUS' ENTERED AT 09:19:43 ON 21 JAN 2003

FILE 'BIOSIS' ENTERED AT 09:20:07 ON 21 JAN 2003

L53 500 S L4  
E GERRITSEN M/AU  
L54 0 S E3,E5,E15,E16 AND L53  
E SLIWKOWSKI M/AU  
L55 20 S E3,E5-E7,E9 AND L53  
SEL DN AN 3 4 17  
L56 2 S L55 AND PATENT/DT  
L57 3 S E1-E6  
L58 5 S L56,L57  
L59 5 S L53-L58 AND L58  
L60 8 S L53 AND SMOOTH(L)MUSCLE  
L61 433 S L53 (L) RECEPTOR  
L62 7 S L61 (L) ANTAGON?  
L63 102 S L61 (L) INHIBIT?  
L64 4 S L59 AND L60-L63  
L65 5 S L59,L64

FILE 'BIOSIS' ENTERED AT 09:29:24 ON 21 JAN 2003

FILE 'MEDLINE' ENTERED AT 09:30:09 ON 21 JAN 2003

L66 354 S L4  
E CELL PROLIFERATION/CT  
E PROLIFERATION/CT  
E CELL MIGRATION/CT  
E E5+ALL  
L67 4939 S E8  
E CELL MIGRATION/CT  
E E3+ALL  
E E2+ALL  
L68 28028 S E4  
L69 56516 S E4+NT  
L70 167713 S CELL?(L)?PROLIFERAT?  
L71 0 S L66 AND L67  
L72 14 S L66 AND L68,L69  
L73 84 S L66 AND L70  
L74 18 S L66 AND CELL?(L)?MIGRAT?  
L75 98 S L72-L74  
E SMOOTH MUSCLE CELL/CT  
E E4+ALL  
E E2+ALL  
L76 4 S L66 AND E3+NT  
L77 0 S L66 AND E13+NT  
L78 24 S AI/CT AND L66  
SEL DN AN 2 16  
L79 2 S L78 AND E1-E6  
E RECEPTOR PROTEIN-TYROSINE KINASES/CT  
E E3+ALL  
L80 375 S E14(L)AI/CT  
L81 1 S L80 AND L66  
L82 2 S L79,L81 AND L66-L81

FILE 'MEDLINE' ENTERED AT 09:39:06 ON 21 JAN 2003

L83 E GERRITSEN M/AU  
0 S E3,E5,E10 AND L66  
E SLIWKOWSKI M/AU

L84 18 S E3,E5,E6 AND L66  
SEL DN AN 3  
L85 1 S E1-E3

FILE 'WPIX' ENTERED AT 09:42:20 ON 21 JAN 2003

L86 40 S (ERBB4 OR ERBB 4 OR ERB B4)/BIX  
L87 5 S L86 AND (SMOOTH(L)MUSCL?)/BIX  
L88 10 S L86 AND ?STENOS?/BIX  
L89 9 S L86 AND A61K039-395/IC, ICM, ICS  
L90 6 S L86 AND C07K016/IC, ICM, ICS  
L91 13 S L86 AND (B14-H01B OR C14-H01B OR B12-G07 OR C12-G07 OR B14-J0  
L92 28 S L86 AND (P520 OR P526 OR P633)/M0,M1,M2,M3,M4,M5,M6  
L93 7 S L86 AND (GERRITSEN ? OR SLIWKOWSKI ?)/AU  
L94 13 S L86 AND (B04-G01 OR C04-G01 OR B04-G04 OR C04-G04 OR B04-B04C  
L95 36 S L87-L94  
L96 13 S L94 AND L95  
SEL DN AN 1 3 5 6 7 8 11 12  
L97 8 S E4-E21  
L98 10 S L93,L97  
L99 25 S L86,L95 NOT L96-L98  
SEL DN AN 8 10 11 12 16 17 19 20 21 22 25  
L100 11 S E22-E46  
L101 21 S L98,L100  
L102 21 S L86-L101 AND L101  
L103 21 S L102 AND (ANTI OR ANTIBOD? OR ANTAGON? OR INHIBIT?)

FILE 'WPIX' ENTERED AT 10:18:11 ON 21 JAN 2003

FILE 'DPCI' ENTERED AT 10:19:00 ON 21 JAN 2003  
E WO2002018444/PN